CLINICAL PHARMACOKINETICS AND PHARMACODYNAMICS

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INTRODUCTION

Therapeutics relates drug administration to physiological effects, both beneficial and toxic, in patient populations. The important intervening steps or processes, which occur following drug dosing that lead to therapeutic effects in the body, are described in Fig. 1. This scheme illustrates the dose-effect relationship. The discipline of pharmacokinetics provides an understanding of drug absorption, disposition, and elimination, as these relate to the physiological effects of drugs. Pharmacodynamics relates the measured response, either efficacious, toxic, or both, to the drug's pharmacokinetics. Pharmacokinetics has become increasingly important, as it has proven to be a very useful tool in understanding not only drug dosage in relation to achievable drug concentrations in plasma, but also the influence of disease states on the behavior of a drug in the body. A very powerful interpretative instrument becomes available when the disciplines of pharmacokinetics and pharmacodynamics are combined. Clinical pharmacokinetics specifically deals with optimizing drug dosage in individual patients. By using plasma concentration measurements, and clinical pharmacokinetic principles, doses can be adjusted to achieve maximal therapeutic utility, with minimum toxic risks for individual patients.

Basic knowledge of pharmacokinetic principles is important not only for the clinician to understand basic drug–patient interrelationships, but also for the drug industry to facilitate the design of relevant studies for drug discovery candidates. The gain from designing proper pharmacokinetic studies can probably be counted not only in better therapy for the patient but also in long-term economic savings for the pharmaceutical industry.

In this article the basic principles of pharmacokinetics and pharmacodynamics will be addressed, and examples of how these principles can be used to increase the understanding of drug therapy and drug dosage formulation are given.

PHARMACODYNAMIC CONSIDERATIONS

The fundamental hypothesis in clinical pharmcokinetics asserts that a relationship exists between a drug concentration in some measurable biologic fluid and observed drug effects, both therapeutic and/or toxic, as illustrated in Fig. 1. Many drugs, for example, antiarrhythmics, anticonvulsants such as phenytoin, and diuretics such as furosemide, show an apparent direct relationship; that is with every change in plasma drug concentration, there is an immediate and corresponding change in effect. For other drugs the relationship is more complicated; the drug level of warfarin for instance, triggers a cascade of events leading to prolonged clotting time. Here, the mean steady-state level rather than the time course of concentrations can be most closely correlated to the therapeutic effect. In some instances, the effect itself is difficult to quantify, and demonstrating any relationship is difficult. When unbound concentrations are maintained at a particular steady-state concentration across a population, then an observed difference in response between individuals must be due to pharmacodynamic receptor-level variability across the population. However, most traditional relationships of drug effects have been developed relative to drug dose rather than steady-state unbound concentrations. When comparing the dose given to the effect, the variability in drug absorption, first-past metabolism, protein binding, and clearance must also be included, thereby giving a significantly more variable and complicated relationship.

The full model for the concentration (C) and effect (E) relationship is the Hill equation, also called the extended E_{max} model (1):

$$E = \frac{E_{max}\, C^s}{EC_{50}^s + C^s} \tag{1}$$

where E_{max} is the maximal effect, EC_{50} is the concentration giving 50% of maximal effect, and s is the slope factor. The Hill equation can be simplified to different extents, for example, if $s = 1$.

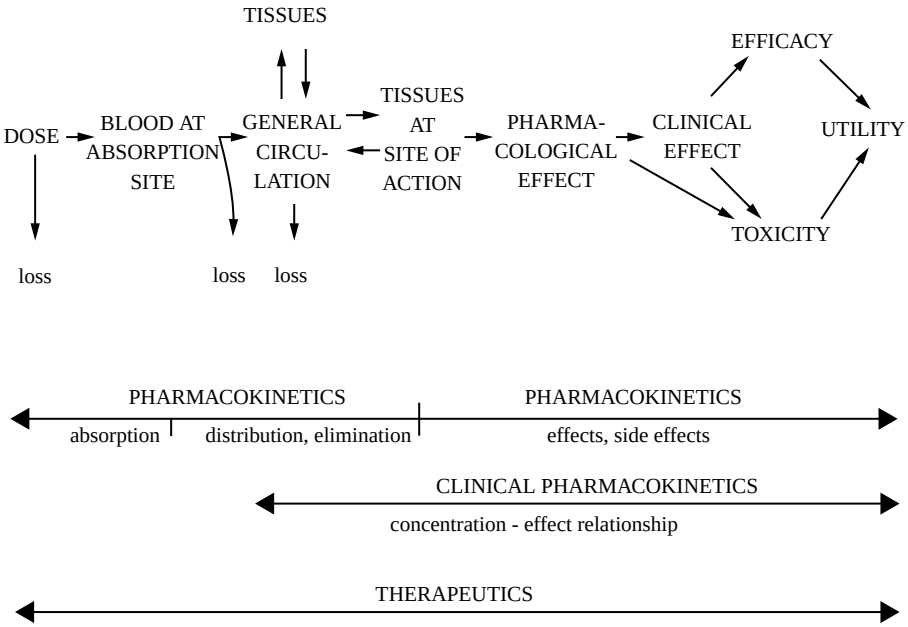

Fig. 1 Schematic representation of the dose-effect relationship for a drug.

Between 20 and 80% of the maximal response, the relationship is logarithmic:

$$E = m \log C + e \tag{2}$$

where m is the slope and e is the intercept. This equation has the limitations of not being able to predict effects outside this range of responses (i.e., $<$20% and $>$80%).

Below 20% of maximal response, the relationship is linear:

$$E = m C + e \tag{3}$$

This relationship has been used for up to 50% of maximal response; however, it then is a coarse approximation, depending upon the value of s (the lower the value of s, the better the approximation).

The Hill equation should be used only when a reasonable estimation of E_{max} is possible and when data are gathered over the whole effect range. If data are available only from the lower part of the curve, the linear equation might just as well be used. The difference between the Hill equation and the linear or log-linear equation is that only the Hill equation gives a mechanistic–physiologic understanding of the effect. The other equations are merely descriptive.

Sheiner and associates (2) have developed the relationship where the pharmacodynamic model (Eq. 1) is integrated together with the pharmacokinetic model. This makes possible describing both the steady-state concentration–effect relationship (i.e., EC_{20}, EC_{50}, EC_{90}, etc.) and the time lag between the measured rapidly changing plasma concentration and the corresponding steady-state effect at that concentration level. This time-lag parameter is described by the equilibration half-time. Using both these parameters, that is, the expected effect and the time required to obtain the effect, allows investigators to model the effect–concentration relationship when patients are not at steady state.

The relationship between the measured effect and steady-state plasma concentration sometimes yields bell-shaped (e.g., nortriptyline) or U-shaped (e.g., clonidine) curves. Several unusual concentration–effect curves, including the U-shaped curve describing the blood pressure lowering effect of clonidine, have been explained by Paalzow and associates (3) as being a result of multiple receptor responses. The drug then acts on several different receptors that can have opposite effects and that are triggered at different concentrations.

Tolerance to the drug effect, that is, a decrease in the effect with time, also obscures the dose-response relationship. Pharmacokinetic and/or pharmacodynamic causes for tolerance development are possible. Pharmacokinetic tolerance, for example, can be caused by induction of metabolic enzymes, thereby causing a decrease in drug concentrations. Pharmacodynamic tolerance can be characterized mainly in two different ways: the receptors down-regulate in response to the drug, giving a smaller response with time, or other physiologic

mechanisms counteract the drug effect. The blood pressure lowering effect of hydralazine that is diminished by a compensatory increase in heart rate, and the diuretic effect of furosemide that is decreased as a result of the drug's volume and salt-depleting actions are two examples.

Fig. 2 illustrates a utility curve, that is, a curve describing the clinical utility of a drug in terms of the risk of side effects from a high concentration and the risk of no effect from a low concentration. The closer the effect and toxicity curves, the more narrow is the range of plasma concentrations that can be used for therapy. The utility is obtained as the difference between the effect and toxicity.

Depending upon the steepness of the concentration–effect relationship (the size of s in Eq. 1), an increase in concentration will result in different changes in effect. An all-or-none relationship is obtained when the curve is very steep ($s > 6$). Theophylline shows a shallow relationship with plasma concentration for its antiasthmatic effect; a big increase in concentration results in a small increase in effect. However, as the side effects of theophylline show a much steeper relationship with plasma concentration, it is critical not to increase theophylline concentrations above 20 mg/L. With a lower limit for antiasthmatic effect of 10 mg/L, theophylline exhibits a narrow range of concentrations where therapy is beneficial.

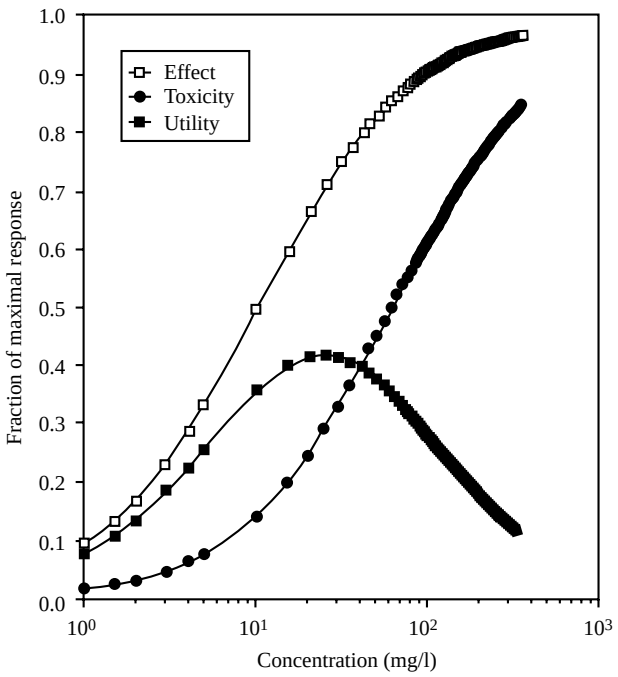

Fig. 2 Utility curve and concentration–effect/toxicity relationships for a theoretical drug according to Eq. (1). EC_{50} for efficacy = 10 mg/L, EC_{50} for toxicity = 60 mg/L, thus the therapeutic index is 6; $s = 1.0$. Utility is obtained as the difference between effect and toxicity.

Another measure of utility is in terms of the ratio between the concentration level causing an undesirable side effect to the concentration level giving the desired therapeutic effect (therapeutic index). For theophylline this ratio is 2, for digoxin it is 1.6, and for furosemide it is 40. The higher the therapeutic index, the less critical are dosing recommendations with respect to the risk of serious side effects.

CLEARANCE

Clearance is the measure of the ability of the body to eliminate a drug, and as such is one of the most important pharmacokinetic parameters, as it gives a well-defined, physiologically relevant measurement of how drugs are eliminated by the organism as a whole, or by a particular organ. Clearance relates drug concentration to the elimination rate from the body (Eq. 4), or at steady state the average concentration C_{ss} to the dosing rate because at steady state the input rate into the body will equal the output rate (Eq. (5)):

$$\text{Elimination rate} = \text{CL}\, C \tag{4}$$

$$\text{Dosing rate} = \text{CL}C_{ss} \tag{5}$$

The clearance concept has been used in defining the pharmacokinetics of drugs since the mid-1970s (4, 5). The clearance concept is based in physiology, where it is used as a measure of renal function (creatinine clearance). Creatinine is formed from muscle breakdown at a constant rate, and thus a constant creatinine concentration in plasma results. The magnitude of this concentration is dependent on the elimination rate of creatinine and the size of the muscle pool (formation rate). By measuring the plasma concentration and the renal excretion of creatinine, renal clearance can be estimated and thereby kidney function indicated, as creatinine is mainly filtered into the urine

$$\text{CL}_{\text{creatinine}} = \frac{\text{Urine volume} \times \text{Urine concentration}}{\text{Plasma concentration}} \tag{6}$$

Drugs are not only eliminated via the kidneys but also eliminated in the bile by the liver and metabolized in the liver and elsewhere, which makes direct measurement of the elimination rate of a drug difficult. Indeed, other routes of elimination could include loss in expired air, saliva, sweat, partition into tissue stores, efflux from the blood into the gut lumen, and gut metabolism as well as

other sites of metabolism such as the lung. The total clearance, CL, can be defined as

$$CL = \frac{Dose_{i.v.}}{AUC} \quad (7)$$

where $Dose_{i.v.}$ is the intravenous dose, and AUC is the resulting area under the plasma concentration time curve. Total clearance can also be measured during continuous drug therapy as dosing rate divided by C_{ss} according to Eq. 5.

Clearance is referenced to plasma (plasma clearance, CL_p), blood (blood clearance, CL_b) or plasma water (unbound clearance, CL_u), depending upon where the concentration is measured. Total clearance can be divided into the contributions of each of the eliminating organs, the most important being renal clearance, CL_R, and hepatic clearance, CL_H.

$$CL = CL_R + CL_H + CL_{gut} + CL_{other} \quad (8)$$

Renal clearance can be separately determined by measuring the excretion rate of unchanged drug into the urine, as for creatinine. The difference between total clearance and renal clearance is usually called *nonrenal clearance*, meaning the clearance that is not accounted for by excretion of unchanged drug into urine, be it metabolism in the liver or elimination by any other organ.

Clearance is measured in units of volume per time (ml/min or L/h) and thus is defined using the same units as blood or plasma flow. By definition, clearance gives the volume of plasma (blood) from which a drug is completely removed per unit time. For some drugs the liver or kidneys have the ability to clear drug from all the blood flowing through the organ; for example, *p*-aminohippuric acid (PAH) has a renal plasma clearance of 600–700 ml/min, which equals renal plasma flow. Because PAH does not partition into red blood cells, PAH renal blood clearance will equal renal blood flow (see imipramine in the next paragraph for calculations according to Eq. 9, $C_{RBC}/C_p = 0$). So, when the eliminating organ has a high capacity to eliminate a drug, the blood clearance equals the blood flow to that organ. As the organ cannot eliminate drug any faster than the rate at which drug is presented to the organ, blood flow becomes the limiting value for clearance. Thus, hepatic blood clearance cannot exceed 1.5 L/min, and renal blood clearance cannot exceed 1.2–1.3 L/min.

Some drugs show a higher plasma clearance than the corresponding plasma flow through the eliminating organ. Imipramine has a plasma clearance of 1050 ml/min (6), thus exceeding the rate of plasma flow to the liver, where it is predominantly eliminated. Looking at whole blood, the concentration of imipramine in blood is higher than its concentration in plasma because of a considerable partitioning into red blood cells ($C_{RBC}/C_p = 2.7$). Thus, the amount of drug delivered to the liver by the blood is much higher than that assumed from measuring its plasma concentration alone. The relationship between plasma and blood clearance at steady state is given by

$$\frac{CL_p}{CL_b} = \frac{C_b}{C_p} = 1 + H\left(\frac{C_{RBC}}{C_p} - 1\right) \quad (9)$$

Imipramine blood clearance can be calculated by substituting the red blood cell to plasma concentration ratio and the average value for hematocrit ($H = 0.45$) into Eq. 10). The resulting blood clearance is calculated to be 595 ml/min, a value within the physiologic range of liver blood flow The higher plasma versus blood clearance for imipramine also indicates that the drug present in the red blood cells is readily available for the metabolizing enzymes by being in rapid equilibrium with the drug present in plasma water. Thus, the plasma clearance may assume values that are not "physiologic." However, if the concentration in blood is used to define clearance, the maximal clearance possible is equal to the sum of blood flow to the various organs of elimination. If a drug shows a higher blood clearance than the combined blood flow, a probable cause is extrahepatic or extrarenal elimination, such as the metabolism of nitroglycerin in blood and tissues. The *rate of elimination* of a compound by an organ is the difference between the rate of presentation to the organ and the rate of exit from the organ. *Rate of presentation* equals the organ blood flow multiplied by the entering concentration (QC_{in}), and the *rate of exit* equals the blood flow multiplied by the exiting drug concentration (QC_{out}) (Fig. 3).

$$\text{Rate of elimination} = Q\,C_{in} - Q\,C_{out} \quad (10)$$

By relating the rate of elimination to the entering concentration (Eq. 4), an expression for organ clearance of drug can be obtained

$$CL_{organ} = \frac{Q(C_{in} - C_{out})}{C_{in}} = Q\,ER \quad (11)$$

in terms of blood flow and ER, the extraction ratio, which equals $(C_{in} - C_{out})/C_{in}$. A high organ clearance signifies that the organ has a high capacity to extract drug from the blood.

For a compound for which the organ has a high extraction capacity, the exiting concentration is very low relative to the entering concentration, and ER approaches unity. For an organ with a low extraction capacity, the exiting concentration is not very different from the entering concentration, and ER approaches zero. Extraction ratio can thus be expressed as the fraction of the organ blood flow

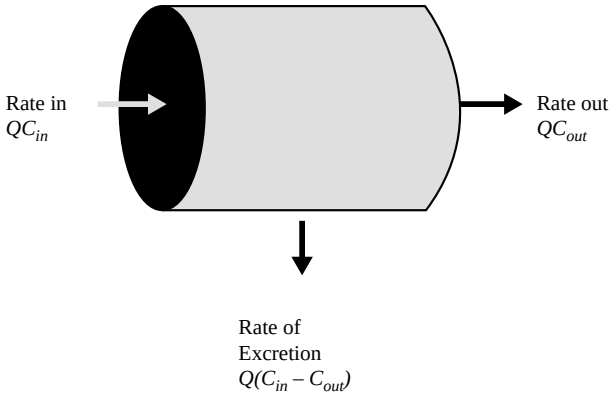

Fig. 3 Extraction of drug in an organ of elimination.

that is cleared by the organ ($ER = CL_{organ}/Q_{organ}$). Several models relating the hepatic clearance to physiologic parameters have been suggested, including the well-stirred and the parallel tube models (7, 8), the distributed model (9, 10), and the dispersion model (11–14). The well-stirred model is the most easily understood and most commonly employed model, and the following discussion will be based on this approach.

The well-stirred model assumes that the unbound drug concentration leaving the organ, for example the liver, is equal to the unbound concentration within the organ, thus assuming an instant "mixing" at the entrance of drug into the organ. The intrinsic ability to metabolize or otherwise clear unbound drug and the protein binding (unbound fraction, f_u) together with the blood flow through the liver (Q_H) all contribute to the resulting hepatic clearance, which may be mathematically expressed as

$$CL_H = Q_H \frac{f_u\, CL_{u,int}}{Q_H + f_u CL_{u,int}} \tag{12}$$

Thus, an example of a high-extraction drug is when the capacity of the liver to metabolize a drug is large compared to the rate at which drug enters the liver ($f_u\, CL_{u,int} \gg Q_H$), clearance approximates liver blood flow

$$CL \cong Q_H \tag{13}$$

An example of low-extraction drug is when the capacity of the liver to metabolize a drug is small relative to the rate of presentation ($f_u\, CL_{u,int} \ll Q_H$), because of a low intrinsic ability to metabolize or because of diffusion problems to the enzyme site. Under these conditions, hepatic clearance approximates

$$CL \cong f_u\, CL_{u,int} \tag{14}$$

Between these extremes, hepatic clearance is dependent on all three factors: Unbound fraction of drug, intrinsic clearance, and hepatic blood flow. The unbound clearance, CL_u, equals CL/f_u.

A reasonable assumption is that the active secretion mechanism in the kidney can also be described by the well-stirred model. However, the kidneys have several mechanisms that may determine renal clearance of a drug, including passive filtration and reabsorption.

The renal clearance is the sum of filtration and secretion minus reabsorption. It can be described as

$$CL_R = CL_{filtration} + CL_{secretion} - CL_{reabsorption} \tag{15}$$

or,

$$CL_R = (CL_{filtration} + CL_{secretion})\,(1 - \text{fraction reabsorbed}) \tag{16}$$

Filtration in the kidneys is determined by the glomerular filtration rate, GFR (120 ml/min in a healthy young person), and by the fraction of the drug that is dissolved in plasma water, that is, the unbound fraction, f_u. Thus,

$$CL_{filtration} = f_u\, GFR \tag{17}$$

Suppositions regarding the mechanisms by which a drug is renally eliminated can be made by comparing the filtration clearance with the measured renal clearance. Drug is always passively filtered to some extent, depending of the value of f_u. If $CL_R > CL_{filtration}$, the drug is also secreted and may be reabsorbed but to a smaller extent than it is secreted. If $CL_R < CL_{filtration}$, however, this is an indication of reabsorption but does not exclude secretion. If $CL_R = CL_{filtration}$, the drug can still be both secreted and reabsorbed, but to the same extent. Conclusive evidence on whether a drug is reabsorbed cannot be made solely on the basis of clearance values.

Intestinal Metabolism or Clearance

Recently, it has been recognized that small intestinal metabolism and active efflux of orally absorbed drugs, are major determinants of oral drug bioavailability (15). Many elements, including patient specific ones, determine the extent of oral drug delivery. The observed oral bioavailability (F_{oral}) of any particular drug is dependent upon the following processes: delivery to the intestine (gastric emptying, pH, presence of food), absorption from the lumen of the intestine (dissolution, lipophilicity, particle size, active uptake), intestinal metabolism (phase I/phase II), active extrusion (drug efflux pumps), and then first pass hepatic metabolism (16).

The enzymes of the cytochrome P 4503A family are the predominant phase I drug metabolizing enzymes in man. The major isoform of the CYP3A family is CYP3A4, the

predominant form found in adult human liver and small intestine. Members of the 3A4 family are estimated to be responsible for the metabolism of more than one half of all drugs that are substrates for the P450 system of metabolic enzymes in man (17). The levels of CYP3A4 found in human liver and small intestine is highly variable, with 10–100 fold variations observed in liver and as much as 30-fold variation in the small intestine, respectively (18). Levels of CYP3A4 in the small intestine are generally 10–50% of the levels found in the human liver, and these levels as well as the activity of the enzyme decrease longitudinally along the small intestine (19). The enzymes of the CYP3A4 subfamily comprise approximately 30% of all hepatic cytochromes and at least 70% of all intestinal cytochromes responsible for drug metabolism (20).

Previously, drug absorption from the gut was assumed to occur by passive processes, and little attention was paid to the activity of counter transport systems. It has now been recognized that P-glycoprotein (P-gp), an ATP-dependent efflux transporter, is expressed at high levels on the apical surface of the columnar epithelial cells in the jejunum of the small intestine (21). P-gp represents the best studied member of the ATP binding cassette (ABC) family of transporters, and is the product of the multidrug resistance gene MDR1 in man. P-gp is expressed in a wide variety of tissues including the adrenal glands, the bladder, the cells of the blood–brain barrier, kidney, liver, lungs, pancreas, rectum, spleen, and most importantly for the purpose of oral bioavailability, in the esophagus, stomach, jejunum, and colon (21–23). In an apparent contrast to the situation noted above for CYP3A, levels of P-gp increase longitudinally along the intestine, with the lowest levels found in the stomach and the highest levels found in the colon (23).

The co-importance of CYP3A and P-gp for the oral bioavailability of drugs is suggested by their shared locations within the enterocytes of the small bowel, as well as a significant overlap in their substrate specificities (21, 24–28). Intracellularly, P-gp is found traversing the plasma membrane of enterocytes while CYP3A is found within the cytoplasm on the endoplasmic reticulum. Although gene expression of these two proteins does not appear to be coordinately regulated (29, 30), their proximal spatial relationship suggests that P-gp may act to regulate exposure of drug (substrates) to metabolism by CYP3A. Repeated absorption and extrusion processes would then, result in repeated exposure of drug to CYP3A, resulting in enhanced overall metabolism, and correspondingly lower oral bioavailability, as depicted in Fig. 4. This spatial juxtaposition, coupled with the large number of overlaps between CYP3A and P-gp substrates, suggests a strong

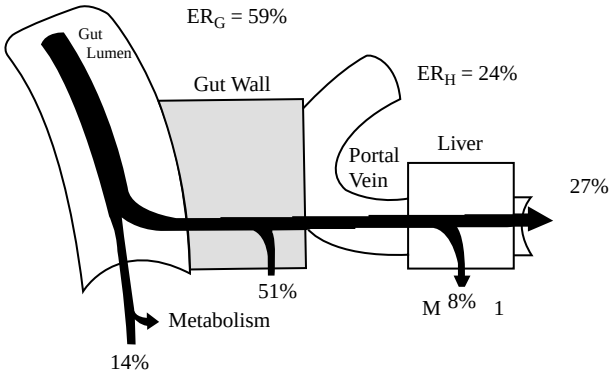

Fig. 4 This cartoon depicts the various processes leading to an oral bioavailability of 27%, following an oral dose of the Sandimmune® formulation of cyclosporine (15). The values at the bottom of the figure indicate the average fraction of the dose lost in each of the processes; i.e., 14% of the dose is either unabsorbed, counter transported (effluxed) by P-gp, or degraded in the gut lumen, 51% of the drug is metabolized in the enterocytes of the gut wall, and only 8% is lost due to hepatic first-pass metabolism.

complementary role for these proteins in the pharmacokinetics of drug absorption.

Oral bioavailability (F_{oral}) is equal to the product of the fraction of dose absorbed (F_{abs}), the fraction of the absorbed dose which passes into the hepatic portal blood flow unmetabolized (F_G), and the hepatic first-pass availability (F_H), as seen in Eq. 18.

$$F_{oral} = F_{abs}\, F_G\, F_H \tag{18}$$

Gut and hepatic availability may be defined as one minus the extraction ratio (ER) at each site.

$$F_{oral} = F_{abs}(1 - ER_G)(1 - ER_H) \tag{19}$$

The hepatic extraction ratio (ER_H) can be determined after intravenous dosing from the ratio of hepatic clearance (CL_H) to hepatic blood flow (Q_H).

$$ER_H = \frac{CL_H}{Q_H} = \frac{f_u CL_{u,int}}{Q_H + f_u CL_{u,int}} \tag{20}$$

$$\text{So that } F_H = \frac{Q_H}{Q_H + f_u\, CL_{u,int}} \tag{21}$$

The ability to estimate the gut extraction ratio requires further experimental manipulations and assumptions, such as evaluating the effects of an enzyme inducer, e.g., rifampin, on oral and i.v. drug dosing as first utilized by Wu et al. (31) for cyclosporine, or measurement of portal concentrations as first utilized by Thummel and co-workers (19) for midazolam.

It is apparent that the greatest impact on oral bioavailability, that would result from the concerted activity of intestinal CYP3A and P-gp, will be observed in drugs that are characterized by low to intermediate hepatic first-pass extraction. High hepatic extraction will probably obscure the gut effects. The inhibition or induction of intestinal CYP3A directly translates into changes in the oral bioavailability of drugs. Inhibition and induction of P-gp in contrast, manifests as a change in the rate of absorption, T_{max}, which can also affect the extent of oral availability, since the T_{max} changes reflects the access of the drug to the intestinal enzymes.

Many commonly prescribed drugs are joint substrates for CYP3A and P-gp, which as has been discussed, both reside in the human intestine, associates within the enterocytes. It is therefore very likely that changes in bioavailability for a number of drugs could result from intestinal metabolism and/or efflux counter transport of absorbed drug back into the intestinal lumen. Selective inhibition of one or both of these processes could theoretically increase bioavailability, while decreasing the variability inherent in absorption. An approach using specific modifiers of intestinal metabolic and counter transport activity could conceivably transform the therapeutic efficacy of many drugs now in use.

DISTRIBUTION

The systemic circulation transports drug molecules from the site of administration to all tissues and organs in the body. Depending upon the physicochemical properties of the drug (lipophilicity, degree of ionization), the drug partitions into different tissues to different extents.

The rate at which distribution takes place into a tissue is dependent on both the drug partition coefficient (concentration in tissue/concentration in blood at equilibrium) and the blood flow to that tissue. The higher the perfusion rate (blood flow per unit volume of tissue), the more rapid is equilibrium achieved between blood and tissue. The higher the partitioning into the tissue, the longer reaching equilibrium takes, as more drug has to be transported to the tissue.

Within the blood, drug is dissolved in the plasma water (unbound concentration, C_u). Drug can also be bound to plasma proteins and concentrated in the red blood cells. It is the unbound drug molecules that diffuse across the membranes into the tissues. At equilibrium, the unbound concentration of drug is thought to be the same throughout the whole body.

Volume of Distribution

To measure drug concentrations, a blood sample is centrifuged and the plasma concentration analyzed. The relationship between the amount of drug in the body and the concentration (C) is called volume of distribution:

$$V = \text{amount in body}/C \tag{22}$$

Depending on the fluid being measured, blood (C_b), plasma (C_p) or plasma water (C_u), different values for the volume term can be obtained as the concentrations in these fluids differ.

The volume of distribution is a proportionality constant. It can be smaller or larger than the true physiologic fluid spaces of the body, depending upon whether the affinity of the drug is highest in plasma constituents or in other tissues. For a normal 70-kg man, the plasma volume is 3 liters, blood volume is about 5.5 liters, extracellular fluid outside plasma is 12 liters, and total body water is approximately 42 liters.

To determine the volume of distribution of a drug, an i.v. dose is necessary. The volume of distribution can be calculated from the plasma concentration versus time data by means of noncompartmental methods as described by Benet and Galeazzi (32) for a bolus i.v. dose

$$V_{ss} = \frac{\text{Dose}_{\text{i.v.}}\,\text{AUMC}}{\text{AUC}^2} \tag{23}$$

Here V_{ss} represents the volume in which a drug would appear to be distributed during steady state, AUC is the area under the plasma concentration time curve, and AUMC is the area under the first moment of the plasma concentration time curve, that is, the area under the curve of the product of time, t, and plasma concentration, over the time span zero to infinity. The volume of distribution at steady state can also be determined by compartmental methods, that is, by using the coefficients and exponents of a multiexponential fit to the data (33).

An alternative measure of volume of distribution is V_{area}. This parameter is dependent on the terminal half-life or, expressed differently, the terminal rate constant λ_z, where λ_z, is equal to $0.693/\ t_{1/2}$

$$V_{area} = \frac{\text{Dose}_{\text{i.v.}}}{\lambda_z\,\text{AUC}} = \frac{\text{CL}}{\lambda_z} \tag{24}$$

as $\text{Dose}_{\text{i.v.}}/\text{AUC} = \text{CL}$, according to Eq. 7a. Although V_{area} is a convenient and easily calculated parameter, the value of V_{area} can show differences when the half-lives differ, for example, between different patient populations, without a true difference in the distribution space. Contrary to V_{area}, V_{ss} is theoretically independent of changes in elimination. Thus, to determine whether a particular disease state is

Table 1 Pharmacokinetic parameters for cefamandole in normals and uremics

Parameter	Normals[a]	Uremics[b]	Significance
CL (ml/min kg)	2.81 +/− 0.98	0.115 +/− 0.023	$p < 0.05$
$t_{\frac{1}{2}}$ (h)	1.2 +/− 0.2	13.0 +/− 4.5	$p < 0.05$
λ_z (h^{-1})	0.576 +/− 0.096	0.0534 +/− 0.0187	$p < 0.05$
V_{area} (L/kg)	0.298 +/− 0.104	0.138 +/− 0.048	$p < 0.05$
V_{ss} (L/kg)	0.161 +/− 0.050	0.134 +/− 0.045	n. s.

Data is +/− S.D.
[a]Data from Ref. (34).
[b]Data from Ref. (35).

influencing the clearance process and/or the distribution of the drug, the V_{ss} volume term should preferentially be used. An example of the different conclusions that can be drawn, depending on which of these volume terms is used, is shown in Table 1. The pharmacokinetic parameters for cefamandole in six normal volunteers (34) and in three uremic patients (35) are compared. As cefamandole is almost exclusively eliminated via the kidneys, uremia results in a dramatic decrease in clearance (24-fold). The terminal half-life increases, but only by a factor of 11, resulting in more than a twofold difference in V_{area} between the two groups (Eq. 24). Based on these data, conclusions could be made that a decreased renal function not only influences the ability to excrete cefamandole but also results in a decrease in the distribution of the drug in the body. However, when comparing V_{ss} the conclusion is that no significant difference exists in the distribution of cefamandole between the two patient populations.

HALF-LIFE

Half-life is the "oldest" and best known of all pharmacokinetic parameters. It is a measure of the time required for the amount of drug in the body to decline to half of its value. Half-life is a useful measurement to determine the time to reach steady state for chronic dosing, or the time for the amount or concentration of drug to decline, for example, after an intoxication. To reach 90% of steady state or to eliminate 90% of the drug from the body takes 3.3 half-lives because 50% of the steady-state level is reached in one half-life, 75% in two, 87.5% in three, and 93.75% in four half-lives. The corresponding values hold for elimination of drug from the body.

Half-life can be readily determined from a plot of log plasma concentration versus time and was for many years considered to be the most important characteristic of a drug. Early studies examining drug disposition in disease states were compromised, by a reliance on half-life as a sole measure of disposition changes. It is now appreciated that half-life is a secondary, derived parameter that relates to and depends on the primary parameters of clearance (CL) and volume of distribution (V) according to the following relationship in Eq. 25:

$$t_{1/2} \approx \frac{0.693\,V}{\mathrm{CL}} \tag{25}$$

Thus, to look at half-life only as a measure of, for instance, the effect of liver disease on drug pharmacokinetics is not sufficient, as a change in half-life can be caused by either a change in clearance or a change in volume of distribution. Furthermore, half-life may be unchanged in a particular disease state due to parallel changes in both V and CL.

Clearance and volume of distribution are two separate and independent characteristics of a drug. They are closely correlated with physiologic mechanisms in the organism (thereby the term primary parameters). Clearance defines the body's ability to remove the drug, that is, by metabolism or by renal or biliary excretion. Volume of distribution is a measure of the physical interrelationship between the drug and body constituents, such as binding to plasma proteins or partition into muscle, tissue, or fat.

PROTEIN BINDING

At steady state, the distribution of any drug in the body is dependant upon its binding to plasma proteins, blood cells and tissue receptors. Only unbound drug is capable of entering and exiting from plasma and tissue compartments. Therefore, an apparent volume of distribution can be expressed as follows (36),

$$V = V_p + V_{TW}\frac{f_u}{f_{u,T}} \tag{26}$$

where V_p represents the volume of plasma, V_{TW} is the volume of tissue fluid (nonplasma), f_u represents the

Table 2 Conditions that alter the concentration of two major plasma proteins

Plasma protein	Condition	Change in concentration
Albumin	Hepatic cirrhosis	Decrease
	Burns	
	Nephrotic syndrome	
	End stage renal disease	
	Pregnancy	
α_1 Acid glycoprotein	Myocardial infarction	Increase
	Surgery	
	Crohn's disease	
	Rheumatoid arthritis	
	Trauma	

(Adapted from Ref. 40.)

fraction unbound in plasma, and $f_{u,T}$ is the fraction unbound in tissue. Human plasma contains over 60 proteins. Albumin is the major component of this protein family responsible for the binding of most drugs in plasma. Acidic drugs bind primarily to albumin, the major drug-binding protein in plasma. Some acidic drugs bind with very high affinity, for example, furosemide, which is 98–99% bound and warfarin, which is 99.5% bound. Basic drugs bind to albumin with lower affinity but are more avidly bound to proteins like α_1-acid glycoprotein and various plasma lipoproteins. These proteins have lower concentrations in plasma relative to albumin. Binding is therefore more easily saturable, as is the case with some drugs such as prednisolone and disopyramide, yielding fluctuations in the free fraction of drugs falling within the therapeutic plasma concentration range (6). Because the binding of drugs to plasma proteins and tissue binding sites is largely nonselective, many drugs with similar chemical properties can compete with each other for access to binding sites. The concern over the potential for adverse drug events based on competitive displacement from plasma protein binding sites has been overstated however. Indomethacin has been shown to markedly decrease warfarin binding to human serum albumin, in vitro (37). However, this in vitro drug interaction has not been confirmed by in vivo studies (38). Steady-state unbound drug concentrations in vivo are largely independent of factors which alter protein binding, unless a drug is very highly protein bound, for example, greater than 90% (39). A dynamic equilibrium exits between tissue and plasma stores of any drug. Binding at these sites is reversible and changes so rapidly that equilibrium is re-established within milliseconds. Therefore, changes in the free fraction of drugs brought about by competition with higher avidity ligands or saturable kinetics are quickly compensated for by movement of drug from tissue stores into plasma, precluding the need for adjustment of dosage regimens.

Variation in plasma protein concentrations can occur secondary to decreased albumin concentrations associated with hepatic cirrhosis, and nephrotic syndrome (Table 2). Increased (α_1-acid glycoprotein concentrations are associated with the stress response to disease states such as myocardial infarction, inflammatory disease, and postsurgically (41). A more relevant problem resulting from competition between drugs for plasma protein binding is the misinterpretation of the measured concentrations of drugs in plasma, as most assays are not able to differentiate between bound and unbound drug (42). Concentration-dependent binding of a drug to a plasma protein is expected when the total drug concentration approaches the protein concentration. For albumin this concentration is 0.6 m*M*, and for α_1-acid glycoprotein in healthy individuals it is 0.015 mM, assuming that one drug molecule binds per protein molecule. For a drug with a molecular weight of 250, this corresponds to concentrations in plasma of 150 mg/L and 4 mg/L, for saturation of albumin and α_1-acid glycoprotein, respectively.

Influence of Protein-Binding Changes on Volume of Distribution

As is obvious from the relationship shown by Eq. 26, a drug which is characterized by a high degree of binding to plasma proteins (i.e., a low f_u) will exhibit a small volume of distribution. Decreases in albumin concentration, for example, may result in a decline in the fraction of drug bound to plasma proteins. The increased amount of unbound drug is then free to distribute to other tissues.

Unlike binding to plasma proteins however, binding to tissue receptors cannot be measured directly. This parameter is generally assumed to be constant. Again, from Eq. 26, this would appear to result in a volume of distribution increase. However, these changes are only important for drugs exhibiting a high degree of binding in plasma (>90%) and an even higher degree of binding in the tissues, that is, drugs with a high volume of distribution. Changes in protein binding will not significantly affect volume of distribution for low V drugs. Note that changes in volume of distribution do not influence the steady-state relationship between dosing rate and average concentration (Eq. 5).

Influence of Protein-Binding Changes on Clearance

If we examine Eq. 12–14, we can see that for drugs with a low extraction ratio (i.e., chlordiazepoxide), Q_{organ} is much greater than $f_{u,}\ CL_{int}$; clearance is then approximated by $f_u\ CL_{int}$. However in the case of a high extraction ratio drug (i.e. lidocaine), $f_u\ CL_{int}$ is much greater than Q_{organ}, and clearance approaches organ blood flow. Therefore, clearance of high extraction ratio drugs is perfusion rate limited, and not influenced by protein binding. Clearance of low extraction ratio drugs, in contrast to Eq. 14, is dependent upon both the fraction unbound and the intrinsic clearance (CL_{int}) of the metabolizing organ, for example, the liver.

THE CONCEPT OF EXPOSURE

Most pharmacokinetic theory has concentrated on explaining changes in clearance and bioavailability in terms of the parameters of intrinsic clearance, blood flow and fraction unbound (Eqs. 12 and 21). Yet the response of a patient to a dose or dosage regimen of a drug is dependent on the patient exposure to the drug, which is best characterized by AUC. Thus, it will be useful to consider the importance of individual parameters such as CL_{int}, Q and f_u in terms of exposure concepts. Consider first an intravenous dose of a drug where from Eq. 7a

$$AUC = \frac{Dose_{i.v.}}{CL} \tag{27}$$

and for a drug excreted exclusively by the liver substitution of Eq. 12 into Eq. (7a) yields

$$AUC = \frac{Dose_{i.v.}(Q_H + f_u\ CL_{u,int})}{Q_H f_u\ CL_{u,int}} \tag{28}$$

For a high extraction ratio compound ($f_u\ CL_{u,int} \gg Q_H$), exposure will be inversely dependent upon hepatic blood flow

$$AUC \cong \frac{Dose_{i.v.}}{Q_H} \tag{29}$$

while for a low extraction ratio compound ($Q_H \gg f_u\ CL_{int}$), exposure will be inversely related to fraction unbound and intrinsic hepatic clearance.

$$AUC \cong \frac{Dose_{i.v.}}{f_u\ CL_{u,int}} \tag{30}$$

However, for an orally administered compound exposure will also be a function of oral bioavailability

$$AUC = \frac{F_{oral}\ Dose_{oral}}{CL} \tag{31}$$

Substituting, Eq. 18 for F_{oral}, Eq. 21 for $F_{H.}$ and Eq. 12 for CL into Eq. 30 above, and simplifying yields the following expression of exposure following an oral dose of a drug where elimination is via the liver.

$$AUC = \frac{F_{abs}\ F_G\ Dose_{oral}}{f_u\ CL_{u,int}} \tag{32}$$

Note that for oral dosing, exposure is inversely related to fraction unbound and intrinsic clearance for all drugs independent of whether they are low or high extraction ratio compounds.

Comparing Eq. 29 and 31 for a low extraction ratio drug where elimination is primarily hepatic, it is obvious that similar oral and i.v. doses will yield similar AUC values, unless the product of $F_{abs}\ F_G$ is low. A drug with $F_{abs}F_G \approx 1$, such as acetaminophen yields similar exposure following both oral and intravenous dosing, and also the variability of exposure will be similar for both routes, since the factors controlling variability, $f_u\ CL_{u,int}$, are the same in each case. Cyclosporine is an example of a low extraction ratio drug eliminated systemically by hepatic metabolism where exposure is markedly less following oral dosing vs. i.v., since $F_{abs}\ F_G$ is so low, in this case due to marked first pass gut metabolism as depicted in Fig. 4. For this drug we would expect variability in exposure to the oral drug to be greater than i.v., due to the addition of the $F_{abs}\cdot\ F_G$ differences.

Propranolol is a good example of a high extraction ratio drug where systemic elimination is almost completely hepatic. Although there is some gut metabolism for propranolol following oral dosing, it is not extensive ($F_G \gg F_H$). Fig. 5 depicts the predicted differences in exposure following i.v. (10 mg) and oral (80 mg) dosing for this high

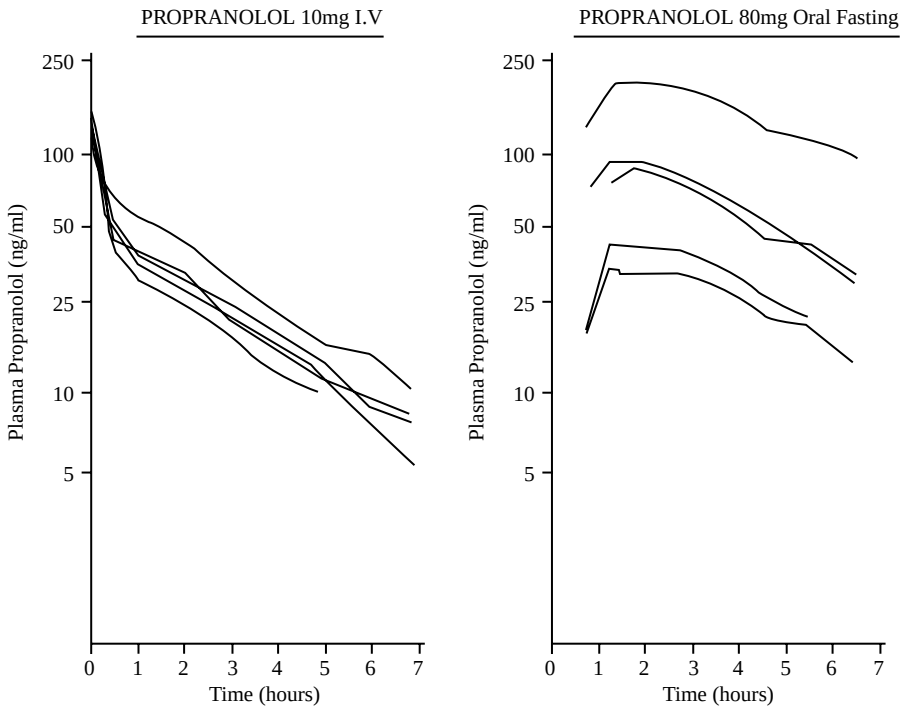

Fig. 5 Plasma propranolol levels in 5 subjects after i.v. administration of 10 mg and oral administration of 80 mg to fasting subjects. Observe the much larger variability in plasma concentrations between individuals after administration via the oral route. (From Ref. 43.)

extraction ratio drug. Note in comparing Eq. 28 and 31 that exposure is less for the oral dose since $f_u\ CL_{u,int} > Q_H$. In addition, it is obvious from Fig. 5 that the variability following oral dosing is much greater than that following i.v. dosing. That is, hepatic blood flow from subject to subject shows much less variability than the intrinsic clearance of the hepatic enzymes.

Returning to pharmacodynamic considerations, it is generally believed that drug responses, both efficacious and toxic, are related to exposure of the patient to unbound concentrations of the drug. For intermittent (not continuous infusion) dosing of drugs, Eq. 1 can be written as

$$E = \frac{E_{max}\ AUC_u^s}{AUC_{u,50}^s + AUC_u{}^s} \tag{33}$$

where $AUC_{u,50}$ is the unbound AUC that yields 50% of the maximal effect over a dosing interval. That is, the effect achieved over a dosing interval for a given dose of the drug is a function of the exposure to unbound concentrations of the drug. Unbound drug exposure is related to total exposure by f_u, fraction unbound.

$$AUC_u = AUC f_u \tag{34}$$

Note that unbound drug exposure will be independent of f_u for orally administered drugs that are predominantly eliminated by hepatic mechanisms. When AUC from Eq. 31 is substituted into Eq. 33 then

$$AUC_u = \frac{F_{abs}\ F_G\ Dose_{oral}}{CL_{u,int}} \tag{35}$$

Similarly for intravenous dosing of low extraction ratio drugs, AUC_u is independent of f_u. Substituting, Eq. 29 into Eq. 33 yields

$$AUC_u \cong \frac{Dose_{i.v.}}{CL_{u,int}} \tag{36}$$

For high extraction drugs predominantly eliminated by the liver, f_u does affect AUC_u

$$AUC_u \cong \frac{f_u\ Dose_{i.v}}{Q_H} \tag{37}$$

For drugs where hepatic elimination is negligible, then $F_H = 1$ and following oral or intravenous dosing we may predict AUC_u as follows

$$AUC_u = \frac{f_u\ F_{abs}\ F_G\ Dose}{CL} \tag{38}$$

and for a drug eliminated by renal processes

$$\mathrm{CL} = \frac{Q_\mathrm{K} f_\mathrm{u}\,\mathrm{CL}_\mathrm{u,int}}{Q_\mathrm{K} + f_\mathrm{u}\,\mathrm{CL}_\mathrm{u,int}} \tag{39}$$

where Q_K is blood flow to the kidney. Substituting Eq. 38 into Eq. 37, then

$$\mathrm{AUC_u} = \frac{F_\mathrm{abs} F_\mathrm{G}\,\mathrm{Dose}(Q_\mathrm{K} + f_\mathrm{u}\,\mathrm{CL}_\mathrm{u,int})}{Q_\mathrm{K}\,\mathrm{CL}_\mathrm{u,int}} \tag{40}$$

For a low extraction ratio drug in the kidney ($Q_\mathrm{k} \gg f_\mathrm{u}$ $\mathrm{CL}_\mathrm{u,int}$), Eq. 39 becomes

$$\mathrm{AUC_u} = \frac{F_\mathrm{abs} F_\mathrm{G}\,\mathrm{Dose}}{\mathrm{CL}_\mathrm{u,int}} \tag{41}$$

wheras for a high extraction ratio drug in the kidney (f_u $CL_\mathrm{u,int} \gg Q_k$), Eq. 39 becomes

$$\mathrm{AUC_u} = \frac{F_\mathrm{abs} F_\mathrm{G}\,\mathrm{Dose}\, f_\mathrm{u}}{Q_\mathrm{K}} \tag{42}$$

Note from the equations above that f_u becomes a determinant of $\mathrm{AUC_u}$, and its thereby effect, only for a high extraction ratio drug given intravenously when the liver is the major route of elimination (Eq. 36), and for a high extraction ratio drug given orally or intravenously when the kidney is the major route of administration (Eq. 41). Since most drug dosings do not fall into these very limited categories, it now becomes clear why changes in protein binding as a function of disease state or drug interactions are generally of irrelevant consequences.

NONLINEAR PHARMACOKINETICS

Most drugs fortunately show linear pharmacokinetics within the therapeutic plasma concentration range (that is, with a doubling of the dose, the plasma concentration is also doubled), making possible the prediction of the impact of changes in drug dosing on the pharmacokinetic outcome.

Nonlinear pharmacokinetics are caused mainly by saturation of the metabolizing enzymes during drug elimination or during the first passage of drug through the liver, and also by saturable protein binding as previously discussed. This leads to less predictable results in drug therapy and to the risk of a higher incidence of side effects.

Nonlinear Elimination/Clearance

All metabolic processes are saturable at a certain concentration of the substrate/drug. Thus, rate of elimination of the drug by metabolism as described by Eq. 5 can also be described by a Michaelis-Menten equation:

$$\text{Rate of metabolism} = \frac{V_\mathrm{m} C}{K_\mathrm{m} + C} \tag{43}$$

From these equations metabolic clearance can be described as

$$\mathrm{CL} = \frac{V_\mathrm{m}}{K_\mathrm{m} + C} \tag{44}$$

where V_m is maximal velocity and K_m is the Michaelis-Menten constant. When kinetics are linear, $C \ll K_\mathrm{in}$, and clearance equals $V_\mathrm{m}/K_\mathrm{m}$, but as the concentration approaches or exceeds Km, clearance becomes dependent on the concentration, resulting in saturable metabolism. At steady state, when input rate (R_in) equals elimination rate, the steady-state concentration can be described by replacing rate of metabolism in Eq. 42 by R_in and rearranging

$$C_\mathrm{ss} = \frac{K_\mathrm{m} R_\mathrm{in}}{V_\mathrm{m} - R_\mathrm{in}} \tag{45}$$

Drugs that show saturable metabolism within the therapeutic range include phenytoin and salicylate. Because of the serious side effects encountered with phenytoin, and because of the genetic variability in metabolic capacity with respect to individual V_m and K_m values, phenytoin therapy is closely monitored using plasma concentration analysis. Phenytoin has a therapeutic concentration range of 10–20 mg/L, which is above K_m for most individuals. A small change of the dose in this region leads to a big change in plasma concentrations. An orbit graph of the relationship between V_m, K_m, and the average steady-state concentration of phenytoin based on Eq. 44 is shown in Fig. 6.

The mean values of K_m and V_m within the population are 4 mg/L and 7 mg/kg/day, respectively. The variation within the population is also depicted in Fig. 6, where 50% of the population has K_m and V_m values within the innermost circle, 75% within the second circle, and so on. With the help of this graph, the suitable dosing rate of phenytoin for an individual patient can be determined. With two plasma concentrations at two different dosing rates of phenytoin in one patient, his/her individual V_m and K_m values can be obtained to further optimize the dosing schedule.

Saturable first-pass effect

Because of very high drug concentrations entering the gut and the liver during the absorption of a drug after oral administration, the liver may often be exposed to drug concentrations that are much higher than after i.v. administration or much higher than the concentrations

Table 3 The extent of urinary excretion of *p*-Aminobenzoic acid and its acetyl metabolite as a function of rate and route of administration in one subject

Route	Total dose Na-PABA (g)	Total PABA in urine in 24 h as % of dose excreted in 24 h (%)	Acetyl-PABA in urine as % of total PABA (%)
i.v. Bolus	1	102	51
Prolonged administration			
i.v. infusion—270 mm	0.4	90	95
10 Oral doses given every half hour	0.4	95	97
Single dose			
Oral solution	1	103	51
	2	103	47
	4	102	36
	8	102	30

(Adapted from Ref 46.)

encountered during the elimination phase after oral administration. These initial hepatic portal vein concentrations after oral administration may exceed K_m even if the plasma concentrations measured in a peripheral venous sample do not exceed K_m. The higher the dose, the more of the drug escapes first-pass metabolism, which gives higher bioavailabiity with increasing dose. An illustrative example of this is the availability of *p*-aminobenzoic acid (PABA) as shown in Table 3 (46). Virtually all PABA is eliminated into the urine as metabolite and unchanged drug within 24 h. However, the percent of the dose that has been metabolized to acetyl-PABA is dependent on dose size and rate of administration, with a clear decrease of the fraction of metabolite formed with increasing dose after oral administration. Also, the fraction of the dose that is metabolized increases dramatically with prolonged oral and i.v. administration. This may also have an impact on slow-release formulations, which for drugs exhibiting a saturable first-pass effect never yield portal vein concentrations as high as comparable immediate-release tablets, thus resulting in lower bioavailabiity for the slow-release formulation.

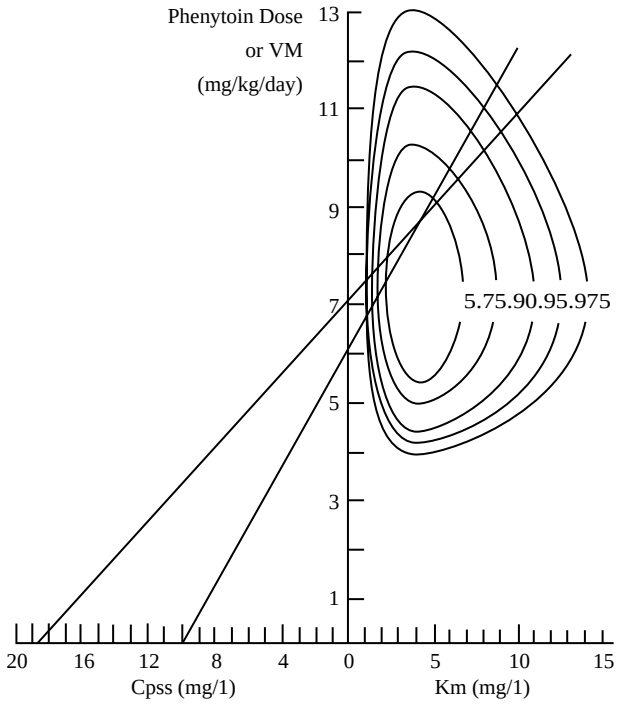

Fig. 6 The Bayesian feedback method of phenytoin dosage prediction. The eccentric circles represent the fraction of the sample population whose V_m and K_m values are within that orbit. By drawing lines from the measured C_{ss} values via the given doses of phenytoin, the most probable values of V_m and K_m can be estimated and further used in calculation of new dosing rates corresponding to a target concentration. (From Ref 44; also discussed in Ref 45.)

STEADY-STATE CONSIDERATIONS IN DESIGN OF DOSAGE REGIMENS

Most drug therapy is designed for chronic drug administration, such as for treatment of hypertension or

diabetes. At steady state, the rate of input equals the rate of elimination (cf. Eqs. 5 and 6):

$$\frac{F\,\text{Dose}}{\tau} = \text{CL}\,C_{\text{ss,avg}} \tag{46}$$

where F is bioavailabiity, τ is the dosing interval, and $C_{\text{ss,avg}}$ is the average concentration during steady state. Note $C_{\text{ss,avg}}$ is another measure of exposure as discussed previously, since during the dosing interval $C_{\text{ss,avg}}$ is equivalent to AUC/τ. Multiplying both sides of Eq. 45 by τ and dividing by CL yields Eq. 30. From Eq. 45 dosing rate can be calculated knowing F and CL, or if $C_{\text{ss,avg}}$ is measured, CL/F can be estimated in a patient. Plasma drug concentration measurements as an aid in giving appropriate drug treatment may be useful when

1. The therapeutic index of the drug is low (e.g., theophylline, digoxin).
2. No pharmacodynamic measurements (e.g., blood pressure, minor side effects such as dry mouth during anticholinergic drug therapy) can be used as end points for therapy.
3. The drug shows nonlinear kinetics within the therapeutic range (e.g., phenytoin).
4. The patient is "uncommon" (e.g., newborns, small children, pregnant women, or patients with decreased kidney function).

For the average steady-state concentration, the frequency of drug administration is not important as long as the dosing rate is the same (Fig. 7). Thus, 1020 mg of theophylline can be given every 24 h or 340 mg every 8 h and still have the same average plasma concentration as when a constant infusion of 43.2 mg/h is given (17). However, the fluctuations around the mean value are influenced by the dosing interval. For drugs with a small therapeutic index, the fluctuations between maximum and minimum concentrations during a dosing interval must be kept within the therapeutic range, thus favoring shorter dosing intervals.

Maximum ($C_{\text{ss,max}}$) and minimum ($C_{\text{ss,min}}$) concentrations during a dosing interval tau (τ) can be estimated using the following equations, assuming rapid absorption compared to elimination, and a one-compartment model for the elimination, where lambda (λ) is the rate constant for drug elimination:

$$C_{\text{ss,max}} = \frac{F\,\text{Dose}/V}{(1 - e^{-\lambda\tau})} \tag{47}$$

In Equation (46) (F Dose)/V describes what is added to the concentration from the new dose. Thus, ($C_{\text{ss,min}}$) may be calculated as ($C_{\text{ss,max}}$) multiplied by the fraction remaining in the body at the end of the dosing interval:

$$\text{C}_{\text{ss,min}} = \text{C}_{\text{ss,max}} e^{-\lambda\tau} \tag{48}$$

The difference between maximum and minimum concentrations at steady state is (F Dose/V), and thus the amount that is eliminated during the dosing interval equals the available dose.

The factors that determine the average concentration at steady state are bioavailability and clearance. The maximum concentration is determined by the volume of distribution, the smaller the volume, the higher the concentration. The dosing interval compared to the half-life is most important in defining the fluctuations. A very convenient dosing interval is equal to the half-life of the drug. This results in a decline during the dosing interval to a minimum concentration that is 50% of the maximal concentration. However, administration of a drug every half-life might sometimes be difficult to achieve because of too short or too long half-lives compared to our 24-h cycle. A practical minimum dosing interval is 6 h, and the maximum is 24 h. For drugs with short half-lives,

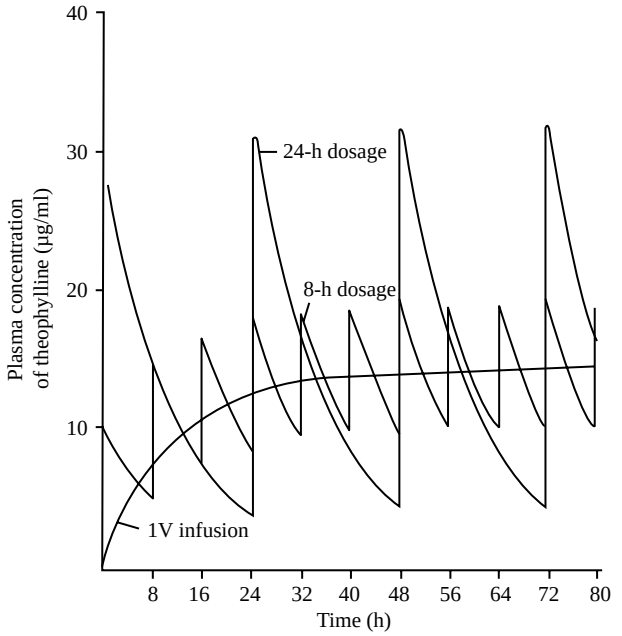

Fig. 7 Relationship between frequency of dosing and maximum and minimum plasma concentrations when a steady-state theophylline plasma level of 15 μg/ml is desired. The smoothly rising line shows the plasma concentration achieved with an intravenous infusion of 43.2 mg/h. The doses for 8-h administration are 340 mg; for 24-h administration, 1020 mg. In each of the three cases, the mean steady-state plasma concentration is 15 μg/ml. (From Ref 47.)

slow-release preparations might give smoother plasma concentration curves and decrease the number of dosings required. Compliance ultimately determines the therapeutic outcome; therefore, adjusting drug dosings to the daily routine of an individual, as much as possible, is important.

Loading Dose

A loading dose is given to attain the effective target concentration rapidly. It can be given as one dose or, more commonly, be divided into several doses over a relatively short period of time, such as one per day. The size of the loading dose depends on the target concentration and the volume of distribution and bioavailability of the drug. The loading dose should give the same amount of drug as will be present in the body during steady state

$$\text{Loading dose} = C_{ss}V/F \tag{49}$$

A loading dose is used when the need for drug therapy is too urgent to wait 3–4 drug half-lives to reach the desired drug concentration in the body. The advantage is a more rapid attainment of steady state. The disadvantage is a higher risk of side effects if the drug concentrations become too high or if the individual is more sensitive to the drug than the average patient. However, in some instances, such as in dosing anti-arrhythmics following an acute myocardial infarction, the only choice is to give a loading dose.

INDIVIDUALIZING DOSAGE REGIMENS: INDIVIDUAL VARIATIONS AND DISEASE STATES

When starting a patient on a particular drug therapy, the clinician is dependent on general dosing information, such as from the PDR (Physicians Desk Reference) or other literature or experience, including an evaluation of the physical status of the patient. At that time the clinician cannot know exactly how this specific patient will react to the drug, pharmacokinetically or pharmacodynamically. For optimal therapy, the progress of therapy should be followed with measurements of relevant effect parameters, by titrating the dose to avoid certain known side effects, or by using therapeutic drug monitoring (drug plasma concentration measurements).

The need for individualized dosage recommendations has received increased attention in recent years parallel to the increased knowledge of what can cause interindividual variability in pharmacokinetic handling of drugs and in pharmacodynamic response. These causes include the influences of genetic variations, age, and disease states. Disease states influence the pharmacokinetics of drugs mainly by impairing drug transport and/or elimination, such as in heart failure or kidney or liver disease.

Kidney function and age show a close correlation. Glomerular filtration rate (GFR) is 100–125 ml/min/70 kg at 20–30 years of age, and then declines approximately 1 ml/min per year as the patient ages. Decreased kidney function as a result of disease is usually detected by measuring serum creatinine levels and calculating the creatinine clearance as a measure of GFR, even though using creatinine as a marker for decreased kidney function has received increased criticism due to overestimation of GFR at medium–low kidney function (48). A GFR between 20 and 50 ml/min indicates moderate renal failure, and values <10 ml/min indicate severe renal failure. If a major portion of the dose of a drug is eliminated unchanged via the kidneys, or if active or toxic metabolites are renally eliminated, corrections for kidney function may be necessary in dosing recommendations.

The influence of age on metabolic clearance is less clear than its influence on renal function. Metabolic clearance is more variable between individuals because of the genetic control and the influence of environmental factors on the metabolic capacity. The term metabolism also encompasses many different enzyme reactions that might be influenced to different extents by age, liver disease, or genetic variables. Unlike renal disease, in which creatinine clearance provides a reasonable estimate of kidney function, not one good indicator exists for the degree of liver function impairment with respect to drug metabolizing capacity.

Liver disease includes many diverse conditions. A distinction can be made between acute and chronic liver disease with respect to changes in clearance. Acute states do not generally seem to influence metabolic clearance of most drugs, but chronic states, such as cirrhosis, seem to decrease metabolic function to a greater degree. Also in cirrhosis, a portion of the blood flow may be shunted past the small capillaries within the liver or bypass the liver, causing even less exposure of the drug to the metabolizing enzymes and thereby greatly increasing the bioavailability of high-extraction-ratio drugs. Different drugs show different behavior with respect to the influence of liver disease on pharmacokinetics. Oxidative pathways seem to be more highly affected by liver disease than conjugation reactions such as glucuronidation. This is evident in the benzodiazepine group, where in cirrhosis patients oxazepam and lorazepam are preferred over diazepam and chlordiazepoxide due to the smaller changes in clearance for the former drugs, which are predominantly glucuronidated (49).

Cardiac failure may influence drug disposition by decreasing the cardiac output and increasing the peripheral resistance, thereby redistributing the blood flow from peripheral organs and tissues, such as kidneys and muscles, in favor of central organs, such as brain and heart. This might cause a slower than normal distribution of drug throughout the body and higher initial concentrations in the central organs that could cause an increased risk of side effects. Because of a lower blood flow to the gastrointestinal tract, heart failure might cause a slower rate of absorption of drugs. However, this seldom results in a lower bioavailability. A decreased and redistributed blood flow in liver and kidneys could yield a slower elimination of highly extracted drugs (50).

Pharmacogenetics

The 20th century yielded an enormous expansion in the chemical arsenal available to medical professionals, for the treatment of disease. The worldwide use of these drugs, particularly over the past several decades, has revealed substantial interindividual differences in the response to drugs. These differences, confirmed and explained by pharmacokinetic analysis, appear in individual patients as variations not only in expected therapeutic responses, but often in the frequency and nature of associated adverse events. Any particular drug or drug dose may be therapeutic in some patients, but ineffective in other individuals. Along the same lines, some individuals may experience drug related adverse effects from standard therapy, while others are unaffected. Recognition of these interindividual differences in drug response is an essential first step in optimizing drug therapy. A great deal of evidence has accumulated over the past several decades indicating that a substantial portion of the observed variability in response to drugs is genetically determined, although age, nutrition, health, and environmental factors play important roles. Pharmacogenetics is primarily concerned with the genetic basis underlying this interindividual drug response, and focuses on genetic differences among individuals, and on the different patterns of drug response among geographically and ethnically distinct populations. The goal of pharmacogenetics is to make truly individualized drug therapy, one could say personalized medicine, possible, and with a reasonably predictive outcome.

The basic unit of inheritance is the *gene*, a specific DNA sequence of base pairs which codes for a particular protein. The *genotype*, is the configuration of genes in an individual, while the *phenotype*, is the outward physical expression of those genes. The mode of inheritance of any individual trait can be either monogenic or polygenic, depending on whether it is derived from a single gene at a single locus (position), or by multiple loci on the chromosomes respectively. An *allele* is one, two or more different forms of the same gene, containing specific inheritable differences, occupying corresponding positions on paired chromosomes. *Genetic polymorphism*, refers to monogenic traits existing in the population in at least two phenotypes, each of which exits at a frequency of at least 1%. An individual possessing a pair of identical alleles for a given trait is said to be *homozygous* for that trait. Individuals who are *heterozygous* for a given trait, possess a combination of dominant and recessive alleles for that trait.

The cytochrome P450 (CYP) monooxygenase system of enzymes is responsible for the primary portion of xenobiotic (foreign substance) metabolism in man. This large family of genes is composed of numerous subtypes, among which CYP2D6, CYP3A4/3A5, CYP1A2, CYP2E1, CYP2C9 and CYP2C19 play especially important roles in genetically determined responses to a wide spectrum of drugs. Examples to date of inherited variability in pharmacokinetics have been almost entirely restricted to drug metabolism. Renal clearance for any drug tends to be very similar for age and weight matched patients in good health. Similarly, the role of genetics in determining the absorption and distribution of drugs is poorly defined.

A number of examples of genetic polymorphisms in drug metabolism have now been identified, involving oxidation, S-methylation, and acetylation., as shown in Table 4. These polymorphisms were initially identified by adverse drug reactions occurring in distinct groups, termed "poor metabolizers," following normal therapeutic doses of the initial, archetypic drugs.

Patients who are homozygous for the CYP2D6 "slow" alleles exhibit a poor metabolizer phenotype, with impaired metabolism and excretion of many drugs, such as metoprolol, nortriptyline and propafone (51). These "poor metabolizers" are more likely to experience adverse reactions to standard doses of these drugs. The frequency of this recessive trait ranges from 1–2% in Asians, approximately 5% in African Americans to 6–10% in Caucasian populations (52). More than 40 drugs now in clinical practice, particularly in the areas of cardiovascular disease and psychiatric disorders exhibit the same polymorphic pattern of metabolism by CYP2D6 (53, 54). Along similar lines, patients who are homozygous for the recessive allele of CYP2C19 are highly sensitive to omeprazole, diazepam, propranolol, mephenytoin, amitriptyline and other drugs metabolized by this isoform (51). The "poor metabolizer" phenotype of CYP2C19 comprises approximately 2–5% of Caucasians

Table 4 Polymorphic drug metabolizing enzymes

Enzyme	Variant phenotypes	Drugs	Modified response
Plasma pseudocholinesterase	Slow hydrolysis	Succinylcholine	Prolonged apnea
Acetyl transferease NAT2	Slow, rapid acetylators	Isoniazid Sulfamethazine Procainamide Sufasalazine Paraminosalicylic acid Hydralazine	Toxic neuritis, lupus erythematosus. (Slow acetylators)
Thiopurine methyltransferase	Poor TPMT methylators	6-Mercaptopurine 6-Thioguanine Azathioprin	Bone marow toxicity, hepatotoxicity
Dihydropyrimidine dehydrogenase	Slow inactivation	5-Fluorouracil	Enhanced toxicity
Aldehyde dehydrogenase	Fast, slow metabolizers	Ethanol	Slow: facial flushing Fast: protection from liver cirrhosis
CYP 2D6	Rapid, poor metabolizers	Debrisoquine Spartein Phenformin Nortriptyline Dextromorphan, etc.	Poor: increased toxicity Rapid: drug resistance
CYP 2C9	Poor metabolizers	Tolbutamide S-warfarin Phenytoin Nonsteroidal anti-inflammatory agents Imipramine	Increased response or toxicity
CYP 2C19	Poor and extensive hydroxylators	Mephenytoin Hexobarbital Omeprazole Proguanil, etc.	Poor: increased toxicity Extensive: drug resistance

and 3–23% of Asians. Another polymorphically expressed enzyme of the P450 superfamily is CYP2C9. This enzyme is responsible for the metabolism of a range of therapeutically important drugs such as phenytoin, tolbutamide and warfarin (5). It has been estimated, that approximately 5% of Caucasians posses the genetic variant of CYP2C9 associated with a fivefold decline in metabolic activity (6). Drugs such as phenytoin and warfarin, for example, have narrow therapeutic indices, and individual genetically based variations in metabolism could have important clinical significance.

Individuals also vary widely in their elimination kinetics of isoniazid, procainamide, and other substrates of N-acetyltransferase (NAT2). Peripheral neuropathy associated with the use of isoniazid, an antituberculosis drug, first surfaced more than 40 years ago. It is now known that the "slow acetylator" phenotype represents approximately 40–50% of Caucasians, and results in decreased clearance of drug with increased potential for associated toxicities.

Genetic heterogeneity appears then, to be an important source of the observed variability in drug response. This strongly implies that information pertaining to interethnic and interindividual genetic differences can play an important role in drug discovery and development. New genetic tools for the rapid, inexpensive determination of patient genotypes could have important therapeutic implications. The need for a new, individualized approach to drug therapy is now, more obvious than ever. Every year approximately 3 billion prescriptions are issued in the United States, of which 2 million result in an adverse reaction, with as many as 1 million resulting in hospitalization. Some 100,000 patients die each year as a result of drug induced adverse

reactions. Early or preventive therapy, guided by individual genetic information, could significantly improve clinical outcomes, while reducing the incidence of drug associated adverse events.

USE OF PHARMACOKINETIC INFORMATION IN DRUG FORMULATION

Depending on the use of a drug, different parameters are important in designing a dosage form. For intermittent drug use, such as aspirin for headache, the ideal dosage form should give a rapid rate of absorption to yield quick relief of the pain. This objective has led to the formulation of buffered or soluble forms of acetylsalicylic acid, for which the absorption rate is limited mainly by the drug's ability to cross the GI membranes. With a different indication, such as aspirin used chronically for rheumatoid arthritis, low exposure to the stomach is desired; for this purpose, enteric-coated tablets and granules of the drug have been formulated.

For a drug intended to be used chronically, the clearance of the drug from the body, together with the extent of availability, determines the dose size for a given therapeutic drug level (Eq. (45)). If clearance and volume of distribution of the specific drug result in a short half-life and keeping drug concentrations above a certain level is important, for example, during antiarrhythmic treatment, the dosing interval is crucial, leading to the demand for a controlled-release dosage form.

However, pharmacokinetic properties of a drug may pose limitations as to the possibility of attaining an ideal therapy. The choice of digoxin over digitoxin is mainly determined by the shorter half-life and in the minds of some clinicians a safer and more predictable drug therapy with digoxin. Oxazepam is an example of a drug with a slower than wanted rate of absorption, which decreases its use as a help in starting to sleep. This slow absorption rate is a characteristic of the drug itself and cannot be increased by drug-product formulation. Thus, dosage form development is limited by the basic pharmacokinetic properties of the drug.

The oral bioavailability of a high-extraction-ratio drug can never be improved by dosage form development if the reason for low availability is high first-pass metabolism. The ability to give an oral dosing regimen of a high-extraction-ratio drug is dependent on the ratio between therapeutic concentrations of the drug and toxic concentrations of the metabolites formed during the first pass and on how critical for successful therapy staying within the therapeutic range of drug concentrations is. Both lidocaine and propranolol have a high extraction in the liver with low bioavailability as a result (35 and 36%, respectively) (6). However, propranolol is given orally and lidocaine is not. Therapeutic concentrations of lidocaine are 1.5–6 mg/L, and side effects start to appear at concentrations of 6–10 mg/L. For lidocaine falling below the therapeutic concentration range is just as serious as going too high in concentration, as both situations may cause arrhythmias. With a half-life of only 1.8 h, oral doses would have to be given very often, which is not practical. Also, the variability in the first-pass effect between individuals (Figs. 4, 5) makes uniform dosing recommendations difficult. Propranolol also has a relatively short half-life (3.9 h), but the therapeutic index is much higher, and plasma concentrations falling below the "therapeutic concentration" are not as critical for the patient; therefore, larger fluctuations in plasma concentrations can be allowed during a dosing interval without loss of an acceptable therapeutic outcome.

The pharmacokinetic profile of a drug can in this way be used as a basis for dosage form development, together with the specific requirements of the particular drug concerning maximal and/or minimal concentrations desired, effectiveness versus toxicity, the desired rate of attaining an effect, and the convenience of drug administration for the individual.

Thus, the knowledge of basic pharmacokinetic features, such as rate of absorption, degree of absorption, degree of renal elimination versus metabolism, whether the drug is a high or a low extraction drug, and the like, and knowledge of the pharmacokinetic–pharmacodynamic relationship are tools in optimizing drug product development to the needs of the patient.

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